Carbon Dioxide Gap as an Endpoint of Post-Operative Haemodynamic Optimisation versus Central Venous Oxygen Saturation in High-Risk Surgical Patients: Aprospective study

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Abstract: Subjective: efficacy of using carbon dioxide gap versus central venous oxygen saturation as an endpoint of hemodynamic optimization in high-risk patients. **Methods and Material**: study was carried out in Tanta University Hospitals in ICU unit from October 2016 to October 2018, Elderly>70years undergoing major surgery, American Society of Anesthesiologist ≥III undergoing major surgery, Complicated major surgery (vascular injury, organ tear), and emergency upper abdominal surgery patients were enrolled in to the study. Patients were randomized into two groups. Group I: patients were hemodynamically optimized to achieve central venous to arterial carbon dioxide gap (ΔCO_2) <6 mmHg. Group II: patients were hemodynamically optimized to achieve central venous oxygen saturation≥70%. **Results:** There was no significant difference as regards demographic data, type of surgery, the total dose of norepinephrine or dobutamine or blood transfused. Organ dysfunction and mortality were significantly lower in group I. values of ΔCO_2 in high-risk surgical patients at admission predicted organ dysfunction better than $ScvO_2$ or serum lactate values. Conclusions: postoperative hemodynamic optimization guided by ΔCO_2 <6mmmHg compared to $ScvO_2$ ≥70% in high-risk surgical patients reduced organ dysfunction, mortality, post-operative complications. Values of ΔCO_2≥6mmHg at admission to ICU predicted organ dysfunction better than $ScvO_2$ <70% or serum lactate ≥2mmol/l.

[Hussin Gamal Elmawardy; Mohamed Samir Abd El Ghaffar; Ghada Fouad El-Baradey and Salah El-Din Ibrahim El-Sherif. **Carbon Dioxide Gap as an Endpoint of Post-Operative Haemodynamic Optimisation versus Central Venous Oxygen Saturation in High-Risk Surgical Patients: Aprospective study.** *Nat Sci* 2019;17(10):70-76]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 9. doi:10.7537/marsnsj171019.09.

Keywords: Carbon Dioxide; Gap; Endpoint; Post-Operative; Haemodynamic; Optimisation; Central Venous; Oxygen; Saturation; High-Risk; Surgical; Patient; Aprospective study

1. Introduction

The mortality rate is higher for high-risk surgical patients compared to other surgical patients. Despite the multiple causes of death and organ failure in those patients, a persistent inadequacy of tissue perfusion is the most critical factor for the development of perioperative organ failure,. Therefore, early recognition and correction of warning signals of persistent tissue hypoperfusion is important [1,2].

Postoperative organ dysfunction was shown to be associated with reduced central venous oxygen saturation ($ScvO_2$), because it explores the balance between oxygen delivery and tissue consumption, but both normal and high values do not exclude the presence of tissue hypoxia if tissue oxygen extraction is impaired [3].

Previous studies have suggested that high serum lactate levels are a warning signal of persistent tissue hypoxia;. However, increase in the lactate level may be delayed compared with other markers of tissue oxygenation adequacy and may be not sensitive enough to reflect a decrease in tissue perfusion [4, 5]. The carbon dioxide gap (ΔCO_2) reflects metabolic alterations resulting from inadequate tissue perfusion. Thus it was hypothesised to be used as a good marker.

The aim of this study was to assess the use of $ScvO_2$ or ΔCO_2 as an endpoint of hemodynamic optimisation in high-risk surgical patients.

The primary outcome of this study was determining the incidence of post-operative organ dysfunction and the secondary outcomes included post-operative complications (nosocomial and surgical wound infection), duration of stay in the intensive care unit (ICU) and mechanical ventilation (MV), and mortality rate.

Methods

This prospective, blinded study was performed at Tanta University Hospitals, Egypt, with approval from the institutional ethics committee, (code 30473/08/15), and (written informed consent was obtained from all participants or their relatives). The patients enrolled in this study were referred to our ICU. All patient data were confidential, with secret codes and a private file for each patient, and the data were used only for the current research.

Inclusion criteria for the study were as follows:

a) Elderly > 70 years old undergoing major surgery;

b) American Society of Anesthesiologists (ASA) ≥ III undergoing major surgery;

c) Complicated major surgery (vascular injury, organ tear); and/or

d) Emergency upper abdominal surgery patients.

We excluded patients who refused to participate, those who had preoperative acute organ failure, and those who did not achieve our goals of resuscitation after 24 hours of ICU admission.

Study design

All patients who met the inclusion criteria were enrolled in the study and were randomised into one of the two groups using a sealed opaque envelope.

Group I (45 patients $\Delta CO2$ group): Patients in this group were hemodynamically optimised to achieve central venous-to- to arterial carbon dioxide tension (Δ CO2) of < 6mmHg.

Group II (47patients ScVO2 group): patients in this group were hemodynamically optimised to achieve ScVO2 ≥70%.

During surgery

Besides our routine hemodynamic monitoring during major surgery, all participants were monitored using a central venous catheter (positioned with the tip within the superior vena cava) and an arterial cannula inserted before the beginning of surgery to obtain repeated blood sampling. Anaesthesia and surgical procedures were conducted according to local standards for medication, anaesthetic technique, and fluid administration. No specific hemodynamic protocol was used during surgery, it is determined by anaesthesiologist.

After ICU admission

Participants were admitted to the ICU immediately after surgery and were managed according to our local standards of care and monitoring (five lead electrocardiography [ECG], pulse oximetry, temperature, and non-invasive blood pressure monitoring), in addition to end-tidal CO2 monitoring in ventilated patients. The central venous line was positioned and verified by chest x-ray.

For all participants, the following two goals must be achieved: (1) The patient must be well oxygenated [oxygen tension (PaO2)≥80 mmHg or oxygen saturation (SpO2) ≥95%] on room air or by oxygen supplementation; (2) Haemoglobin level (Hb) at least-7g/dl.

ΔCO_2<6mmHg in GI and ScvO≥70% in GII were considered to be the 'perfusion indices'.

In each group, if the corresponding index was achieved, no more optimisation was required, and maintenance fluid therapy was given. If the corresponding index was not achieved, a bolus dose of fluids was given (4ml/kg of lactated Ringers solution over a 10- minutes period followed by reassessment over the subsequent 5 minutes, and this was repeated with the aim of reaching this index).

If our goal still not achieved, we assessed the central venous pressure (CVP), and if it was below8mmHg, infusion of a fluid bolus could be repeated, and the mean arterial blood pressure (MAP) was measured. Accordingly, if the MAP was below 65mmHg, nor epinephrine was infused at a constant rate of 0.05 _ 0.3 $\mu g/kg \times min^{-1}$ to achieve the targeted perfusion indices.

CVP was then checked to see if its value was between 8_12 mmHg and was MAP≥65mmHg. If these indices were not achieved, the Hb level increased to reach 10 g/dl in addition to dobutamine infusion (3_10 $\mu g/kg \times min^{-1}$) if needed, and heart rate was monitored closely. If there was persistent failure to achieve the targeted index, O2 consumption was decreased using MV and/or controlling fever, if it was present.

The patient did not meet our inclusion criteria if his/her targeted infusion indices were not achieved within the first24 hours, or if the targeted value was achieved successfully but not maintained for - at least - 6 hours within the first 24 hours of ICU admission.

Patients who failed to achieve the primary goals ($\Delta CO2$ <6mmHg in GI or ScvO2saturation ≥70% in GII) despite optimal hemodynamic stabilisation using crystalloids, packed red blood cells (PRBCs), vasoactive and/or inotropic agents, or if the patient failed to maintain these goals for at least 6 hours during the first day after surgery, they were managed according to the established ICU protocol (i.e., continue supportive treatment and resuscitation after exclusion of any possible surgical complications), and excluded from our study population.

Data collection and measurement

The following information was collected for each registered patient: demographic data, type of surgery, heart rate, mean arterial blood pressure, CVP, $\Delta CO2$ (GI), ScvO2 (GII),Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE II) score within within the first 24 hours of admission, in addition to fluid intake, urine output, and fluid balance after 24 hours of admission. Patients in both groups needed vasopressors or dobutamine and the total dose to be recorded, along with postoperative organ dysfunction, mortality rate, length of MV, duration of ICU stay, and post-operative complications (postoperative intra-abdominal abscesses, wound infections, pneumonia, and urinary tract infections).

Statistical Methods

Statistical presentation and analysis were conducted by SPSS V.24. Quantitative data were expressed using the range, mean, and standard deviation, while qualitative data were expressed using the frequency and percentage. An unpaired t-test was used to compare parametric data (age, weight, and MAP) between the two studied groups. A modified Chi-square test for small numbers was used to compare qualitative data (sex) between two groups. The Mann- Whitney U test was used for comparison of non-parametric data (SOFA score). A *P* value of <0.05 was considered statistically significant. Agreement between the different predictors and the outcome was used and expressed as the sensitivity, specificity, positive predictive value, and negative predictive value. Receiver operating characteristic (ROC) curves were used to show the diagnostic performance of the test, where the area under the curve (AUC) ≥70% indicated acceptable performance. The Youden index was used in conjunction with the ROC curve to detect the optimal cut-off value.

3. Results

The present study included 120 patients who were assessed, and nine patients were excluded because they had preoperative acute organ failure. Thus, 111 patients were randomly allocated into two groups: GI (ΔCO2 group n = 55) and (GII Scvo2 n = 56). Ten patients were then excluded from GI and nine patients from GII because they did not achieve the goal of haemodynamic optimisation at 24 hours after ICU admission. Thus, 45 patients in G1 and 47 patients in GII were analysed in our study.

There was no statistically significant difference between the groups regarding demographic data (age, sex, height, and weight) and type of surgery (Table 1). There were no statistically significant changes between both groups in the mean arterial blood pressure, heart rate, central venous pressure, and serum lactate values at 24 hours after admission, while urine output was significantly increased in GI compared to GII at 24 hours of admission (Table 2).

SOFA score values were significantly lower in GI; while, APACHEII score values were not significantly changed in both groups (Table 2).

Fluid received in GI was significantly higher than that in GII while there was no significant difference between both groups for other therapeutic interventions (total dose of norepinephrine or dobutamine, packed RBCs transfused, and fluid balance). (Table 3)

For the outcome of our study, organ dysfunction, complications, duration of ICU stay and mortality were significantly higher in GII compared to GI (Tables 4 and 5).

The ROC curve (Figs.2, 3, 4, and 5) was used to assess the relationship warning signal at admission and subsequent organ dysfunction. A cutoff value was taken to give the best sensitivity and specificity using the Youden index (Table 6). Δco2 >6.1 mmHg was associated with organ dysfunction, with a sensitivity of 77.8% and a specificity of 69.44%, and the area under the ROC curve was 0.784. A cut-off value of ScvO2 ≤68%was associated with organ dysfunction with a sensitivity of 26.32%, a specificity of 89.29%, and the area under the ROC curve was 0.556. However, a cut-off value of 2.0 mmol/l for serum lactate was associated with a sensitivity of 22% and 42%, and a specificity of 44% and 46% in GI and GII, respectively, which is poor.

Table (1): Demographic data and type of surgery

	Group I	Group II	P. value
Age (years)	60.36± 10.22	63.85 ± 11.75	0.132
Weight	87.28± 23.71	84.17 ± 28.94	0.1044
Sex (M/F)	30/15	28/19	0.481
Height	164.36±16.46	169.85±14.84	0.0646
Type of surgery (Elective/Emergency	27/18	25/22	0.8

*Data presented as mean ±SD

Table (2): Comparison between both groups at the end point of hemodynamic optimization (ΔCO_2<6mmHg in GI and $ScvO_2$ ≥70% in GII) at 24hours of admission. (Mean ±SD)

variables	Group I (ΔCO_2) (n = 45)	Group II (ScvO2) (n = 47)	P
Heart rate (b/m)	85.31± 11.95	86.17±10.75	0.718
Mean arterial Blood pressure (mmHg)	96.02±13.12	94.32±12.66	0.528
Central venous pressure (cm H_2O)	15.16±2.11	14.34±2.0	0.061
Urine Output (ml)	2238.89±647.83	1715.1±522.8	0.0001*
Lactate (mml/l)	0.96±0.46	0.97±0.35	0.380
APACHEII score	8.22±3.89	9.49±5.01	0.2318
SOFA score	1.21±1.45	2.28±2.38	0.0336*

* Statistical significant change (P < 0.05).

Table (3): Comparison between both groups as regard therapeutic interventions. (Mean±SD)

parameter	Group I (ΔCO_2) (n=45)	Group II (ScvO2) (n=47)	P value
fluid received (ml)	3765.55±756.02	3418.08±583.04	0.0152*
Fluid balance (ml)	1527.7±1064.5	1702.9±708.8	0.3534
Packed RBCS transfused (ml)	411±63.25	473±84.19	0.428
the total dose of norepinephrine (mg)	27.16±19.14	24.37±18.67	0.7811
the total dose of dobutamine (mg)	1502.9±312.97	1399.45±785.7	0.8698

* Statistical significant change (P < 0.05).

Table (4) Comparison between both groups as regards to the outcome

	Group I (ΔCO_2) (n=45)	Group II ($ScvO_2$) (n=47)	*P*
ICU Stay (days)	3.27±1.74	4.7±2.75	0.004*
Duration of MV (days)	5.0 ± 3.90	6.02± 4.23	0.415
Organ dysfunction (N)	Single organ (3)	Single organ (1)	0.0459*
	two organs (4)	two organs (11)	
	Three or more organs (2)	Three or more organs (7)	
Complications (%)	13.3%	34.04%	0.0275*
Mortality (%)	2.2%	17.02%	0.0305*

* Statistical significant change (P < 0.05).

Table (5): Comparison between the two studied groups according to post-operative complications

Postoperative Complications	Group I (ΔCO_2) (n = 45)		Group II ($ScvO_2$) (n = 47)		p
	No.	%	No.	%	
Acute renal failure	1	2.2	4	8.5	$^{FE}p=0.404$
Pneumonia	2	4.4	4	8.5	$^{FE}p=0.677$
Abdominal sepsis	5	11.1	8	17.0	0.416
Urinary tract infection (UTI)	0	0.0	2	4.3	$^{FE}p=0.495$
Myocardial infarction (MI)	1	2.2	0	0	$^{FE}p=1.000$
PULM. Embolism	0	0.0	0	0	
Heart failure	0	0.0	0	0.0	-

Table (6): Prediction of CO_2, $ScvO_2$ values at admission to organ dysfunction

Cut off value	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	AUC (95% CI)	Youden index	P value
ΔCO_2(**> 6.1mmHg**)	77.8% (40.0 - 97.2)	69.44% (51.9 - 83.7)	35%	92%	0.784(0.636 - 0.893)	0.472	<0.001
$ScvO_2$(**≤68%**)	26.32% (9.1 - 51.2)	89.29% (71.8 - 97.7)	55%	64%	0.556 (0.404 -0.701)	0.156	0.517

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve, CI: Confidence interval

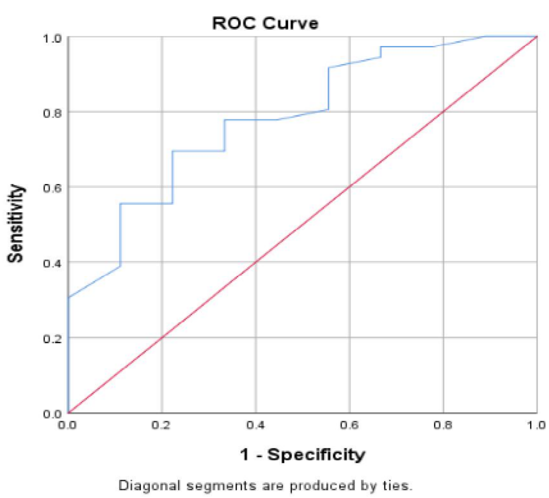

Figure (2): Prediction of CO2 gap at admission to organ dysfunction

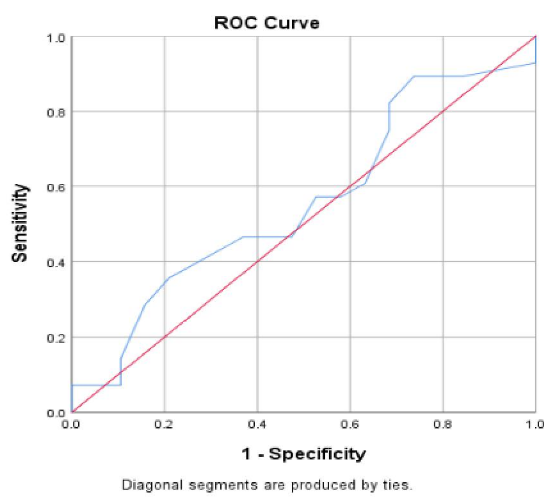

Figure (3): Prediction of $ScvO_2$ at admission to organ dysfunction

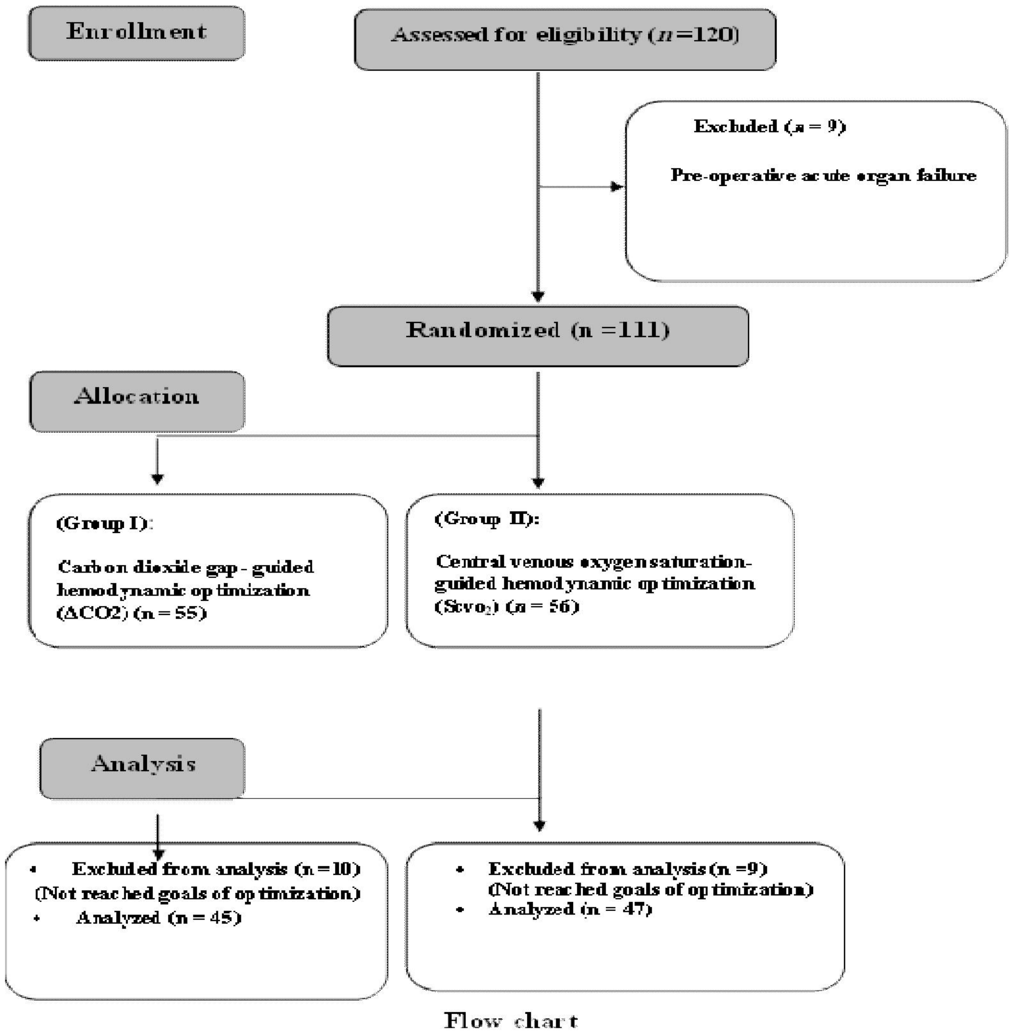

Figure (1): Patient flowchart summarizing enrollment, allocation, follow-up, and analysis

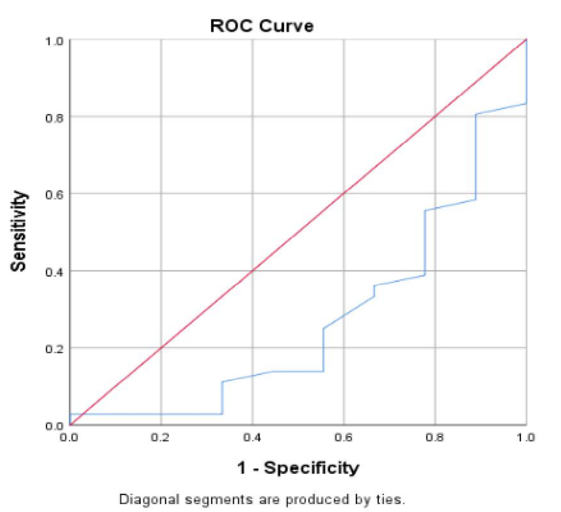

Fig (4): Prediction of Lactate values at admission to organ dysfunction in GI

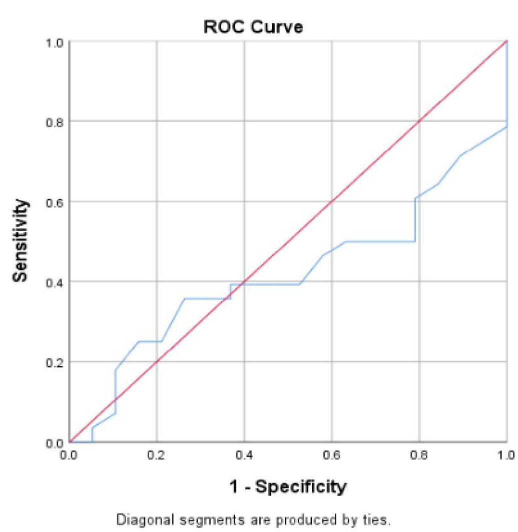

Fig (5): Prediction of Lactate values at admission to organ dysfunction in GII

4. Discussion

One of the principles in high-risk patients is to guarantee adequate tissue perfusion of all organs. Critically ill patients are at greater risk for hypoperfusion compared to healthy people because they have a greater resting energy expenditure and oxygen consumption [(6)].

A key factor in resuscitation is the early detection and treatment of hypovolemia. It is essential to guide fluid therapy without causing significant intravascular volume overload. Several methods of resuscitation have been suggested to determine the outcome in critically ill patients. However, there is no consensus on which approach could be used [(7)].

For the incidence of organ dysfunction, patients with a $\Delta CO2<6$mmHgand who had received hemodynamic optimisation had significantly lessorgan dysfunction. In agreement with our previous study, Benoit Vallet et al. (2008) [(8)]. patients with low $\Delta CO2$ (<6mmHg) had a lower SOFA score at 24 hours after admission compared to patients with a high $\Delta CO2$ (>6mmHg). Additionally, a clinical review by Paul van Beest etal. (2011)[(9)] about the use of venous oxygen saturation as a goal stated that low values warn the clinician about cardio-circulatory or metabolic impairment and should trigger further diagnostics and appropriate actions, whereas normal or high values do not rule out persistent tissue hypoxia.

Moreover, Robin et al (2015)[(10)] concluded that: 1) a high $\Delta CO2$ ($\geq$6 mmHg) was associated with an increased incidence of organ failure and an increase in the duration of MV and length of hospital stay. As long as the increase in the $\Delta CO2$ is secondary to tissue hypoperfusion, then the $\Delta CO2$ might be a useful tool that is complementary to ScvO2 as a therapeutic target. Additionally, Némethet al. (2017) [(11)] found that $ScvO_2$ was affected by fluid resuscitation that is caused haemodilution, which is reflected in the significantly lower level at the end of resuscitation compared to its value at baseline. Therefore, it cannot be used as a single parameter for the resuscitation endpoint.

However, Morel et. al, (2016)[(12)] recorded worse outcomes for patients with a low $\Delta CO2$, as evidenced by a significantly higher SOFA score and mortality rate. The greater difference between this study and ours can be explained by the different type of surgery, and several mechanisms can also lead to organ dysfunction after cardiac surgery, according to their results. Additionally, Pierre-Grégoire et. al, (2017)[(13)] found no association between ΔPCO_2 and postoperative course (morbidity, mortality, SOFA score, length of ICU stay). The absence of an association between the ΔPCO_2 and the patient outcome may be explained by physiopathology of the cardiac surgical population. Moreover, Wittayachamnankul, *et al* (2015) [(14)] studied the role of ScvO2, blood lactate, and $\Delta CO2$ gap as a goal and as a prognostic parameter of sepsis treatment. They concluded that none of these biomarkers can indicate prognosis, predict progression of the disease, or guide treatment in sepsis.

In our study, $\Delta CO2$values at patient admission had a higher predictive value for organ dysfunction than $ScvO_2$. Consistent with results by Robin etal (2015)[(10)], a high PCO2 gap at admission in the postoperative ICU was significantly associated with increased postoperative complications in high-risk surgical patients. Ultimately, Van Beest et al. (2013)[(15)]found that the persistence of a large ΔCO_2gap (greater than 0.8 kPa or 6 mmHg) after 24 hours of treatment was predictive of higher mortality.

5. Conclusion

In this study, postoperative haemodynamic optimisation in high-risk surgical patients guided by $\Delta CO_2<6$mmHg compared to ScvO2$\geq$70% reduced organ dysfunction, mortality, postoperative complications, and length of ICU stay. Values of $\Delta CO_2\geq$ 6mmHg in high-risk surgical patients at ICU admission predicted organ dysfunction better than ScvO2< 70% or serum lactate$\geq$ 2mmol/l.

Conflicts of interest: No conflicts of interest declared.

Authors' Contributions:

All authors had contributed in these study.

Fund: no fund

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7/9/2019